DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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Via Federal Express
WARNING LETTER

Food and Drug Administration
Center for Devices and
Radiological Health
2098 Gaither Road
Rockville, MD 20850

Stephen Smith IV, M.D., Chair
Kaweah Delta Health Care District
Institutional Review Committee
400 West Mineral King 119
Visalia, California 93291

Dear Dr. Smith:

This Warning Letter informs you of objectionable conditions found during a Food and Drug Administration (FDA) inspection of the Kaweah Delta Health Care District Institutional Review Committee (KDHCD IRC), which serves as the Institutional Review Board (IRB) for Kaweah Delta Hospital. This letter also requests that you implement prompt corrective actions. Ms. Marie K. Kinkade and Mr. Thomas W. Gordon, investigators from FDA's San Francisco District Office, conducted the inspection on December 2, 3, 4, 5, and 10, 2003. The purpose of the inspection was to determine whether your activities and procedures as an IRB complied with Title 21, Code of Federal Regulations (21 CFR), Part 50 – Protection of Human Subjects, Part 56 – Institutional Review Boards, and Part 812 – Investigational Device Exemptions. These regulations apply to certain clinical studies of products regulated by FDA.

Our review of the establishment inspection report submitted by the district office revealed serious violations of the above stated regulations. At the conclusion of the inspection, Ms. Kinkade and Mr. Gordon presented a Form FDA 483, "Inspectional Observations," to you; [redacted] Deviations noted on the Form FDA 483, and our subsequent inspection report review are discussed below:

1. **Failure to conduct adequate continuing review of the research. (21 CFR 812.64 and 56.109(f))**

   Pursuant to 21 CFR 56.109(a), IRBs are required to review all research activities covered by FDA regulations in 21 CFR Part 56. Furthermore, to help ensure that the rights and welfare of human subjects are protected, IRBs are required to conduct continuing review of this research at intervals appropriate to the degree of risk, but not less than once per year. (21 CFR 56.109(f))

   KDHCD IRC failed to satisfy these requirements. Examples of this failure include but are not limited to the following:

Your IRB failed to ensure that continuing review of research was conducted on at least an annual basis. For example, your IRB did not conduct continuing reviews of the following studies:

- [redacted]
- [redacted]
- [redacted] and
- [redacted]

2. **Failure to prepare, maintain, and follow adequate written standard operating procedures (SOPs) governing the functions and operations of the IRB. (21 CFR 56.108(a) & (b), and 21 CFR 56.115(a)(6)))**

An IRB must prepare, maintain, and follow written procedures that describe the IRB functions and operations, including: conducting initial and continuing review of research; ensuring that changes to approved research may not be initiated without IRB review and approval, except where necessary to eliminate apparent hazards to human subjects; ensuring prompt reporting to the IRB, appropriate institution officials, and FDA of any unanticipated problems involving risks to human subjects or others and any instances of serious or continuing noncompliance with FDA regulations pertaining to IRBs or determinations of the IRB. (21 CFR 56.108(a), 56.108(b))

- Prior to December 1, 2003, your IRB lacked adequate procedures for:

  Conducting initial and continuing review of research,

  Determining whether an investigation involved a significant or non-significant risk device and which projects required review more often than annually,

  Ensuring prompt reporting to your IRB of changes in research activity, and

  Ensuring prompt reporting to your IRB, appropriate institutional officials, and FDA of unanticipated problems involving risks to human subjects or others, or any instance of serious or continuing noncompliance with FDA's IRB regulations or the requirements or determinations of your IRB.

- On December 1, 2003, the IRB approved new written SOPs which appear to include most of the required elements described above. The new procedures are inadequate, however, in that they do not provide a method to inform clinical investigators of their responsibility to report information to the IRB, such as providing annual reports to the IRB to allow for continuing review, obtaining IRB approval for changes in approved research prior to

implementing (except in limited circumstances), and promptly reporting any unanticipated problems involving risks to human subjects.

3. **Failure to properly utilize expedited review. (21 CFR 56.110(b))**

The IRB may use the expedited review procedure to review minor changes in previously approved research during the period (of one year or less) covered by the original approval. This process allows the review to be carried out by the IRB chairperson or by one or more experienced reviewers on the IRB. The IRB is required to adopt a method of keeping all members advised of research studies that have been approved by expedited review. (21 CFR 56.110(b)-(c))

Your IRB improperly utilized expedited review to renew study approval. On May 28, 2003, over two weeks after the initial IRB approval expired, the chairperson utilized expedited review to renew the [redacted]

4. **Failure to have a majority of IRB members present when reviewing and approving research studies. (21 CFR 56.108(c))**

Each IRB is responsible for ensuring review of proposed research when a majority of the IRB members are present except when using an expedited review procedure. (21 CFR 56.108(c)) You failed to satisfy this requirement on more than one occasion. An example of this failure includes your February 28, 2001 and July 17, 2002 IRB meetings where there was not a majority of members present to review or vote on research proposals. In an effort to satisfy the majority requirement, the IRB Chair was contacted after the February 28, 2001 meeting to submit his vote of approval on the [redacted] study. Since the IRB Chair was not present at the meeting, this did not satisfy the requirement in 21 CFR 56.108(c).

5. **Failure to prepare and maintain adequate documentation of IRB activities. (21 CFR 56.115(a)(1), 56.115(a)(2), 56.115(a)(4) and 56.115(a)(5))**

FDA regulations require that an IRB prepare and maintain adequate documentation of their activities including: copies of all research proposals reviewed; approved sample consent documents; meeting minutes in sufficient detail to show actions taken by the IRB; votes on these actions including how members voted; a written summary of the discussion of controverted issues and their resolution; copies of all correspondence between the IRB and the investigators; and membership rosters containing specific information. (21 CFR 56.115(a))

Examples of your failure to prepare and maintain adequate documentation include, but are not limited to, the following:

- There was no correspondence or records documenting original approvals for the following studies: [redacted]

- Your IRB meeting minutes did not consistently include specific information regarding the IRB's determination of whether studies involved significant or non-significant risk devices, the continuing review and actions taken by the IRB for each study, the frequency of review for each study, and the number of members voting for, against, and abstaining from IRB actions. For example, your meeting minutes for 2001, 2002, and 2003 only show the results of voting on approval of research studies as "M/S/C" (motion, seconded, carried).

- The IRB did not maintain all documents received from clinical investigators, such as the protocols, investigator brochures, advertising, and the approved informed consent forms.

- The following study records were missing: records for [redacted]study, the final report for the "Protocol for [redacted] Study," and the revised approved informed consent form for the [redacted]."

- The IRB membership list for 2003 failed to include two members' earned degrees, representative capacity, experience, and employment or relationship between the members and the institution. The IRB 2002 membership roster also listed an individual as a voting member, even though [redacted] stated during the inspection that this individual was not an IRB member or alternate, and participated only as an ad hoc substitute in the September 18, 2002 and December 9, 2002 IRB meetings.

- Progress reports were missing from the [redacted] study file for 1997, 1998, 1999, 2000 and 2001.

- There was no progress report on file for the [redacted] for 2002.

The deviations cited above are not intended to be an all-inclusive list of deficiencies at your site. As an IRB, it is your responsibility to ensure that your operations are conducted in accordance with applicable FDA regulations.

Within fifteen (15) working days, please respond to this letter in writing. You should be aware that FDA considers the IRB's noncompliant actions to be serious violations of

the law. Failure to respond to this letter and to take prompt action to correct these violations may result in regulatory action without further notice, including initiation of procedures to disqualify the IRB.

Please address your correspondence to the U.S. Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Bioresearch Monitoring, Program Enforcement Branch II (HFZ-312), 2098 Gaither Road, Rockville, Maryland 20850, Attention: Linda Godfrey, Consumer Safety Officer.

A copy of this letter has been sent to FDA's San Francisco District Office, 1431 Harbor Bay Parkway, Alameda, California 94502. We request that a copy of your response also be sent to that office.

If you have any questions, feel free to contact Linda Godfrey at (301) 594-4723 extension 134.

Sincerely yours,

Timothy A. Ulatowski
Director
Office of Compliance
Center for Devices and
Radiological Health

cc:

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